

Clinical, Pathologic, and Immunologic Features of Human T-Lymphotropic Virus Type I–Associated Infective Dermatitis in Children

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Objectives: To define the clinical and laboratory features associated with infective dermatitis (ID) and confirm its association with human T-lymphotropic virus type I (HTLV-I).

Design: A case series of patients with ID were compared with patients with atopic dermatitis (AD), which is an important disease in the differential diagnosis of ID.

Setting: Patients were recruited from dermatology and pediatric clinics at the University Hospital of the West Indies and the Bustamante Children's Hospital, Kingston, Jamaica.

Main Outcome Measures: Clinical and laboratory features of patients with AD were compared with those of patients with ID.

Patients: Consecutive patients older than 1½ years diagnosed as having ID (n=50) and AD (n=35) were enrolled based on clinical findings.

Results: The mean ages of patients with ID and AD were 6.9 and 7.8 years, respectively. Histologically, both diseases were predominantly chronic dermatitis with pro-

pensity for skin colonization with *Staphylococcus aureus* and β -hemolytic streptococci; however, the distribution of sites of skin involvement differed. Infection with HTLV-I was the most distinguishing feature among patients with ID, with seropositive results in 100%; only 5 (14%) of the 35 patients with AD had results seropositive for HTLV-I. Infective dermatitis was further characterized by dermatopathic lymphadenitis in 16 (67%) of 24 patients with palpable nodes. Anemia, lymphocytosis, and low albumin and elevated serum globulin levels were more prevalent among patients with ID. Significant elevations of IgA, IgD, and IgG levels were observed among patients with ID compared with those with AD. However, both patients with AD and those with ID had levels of IgD and IgE elevated above the normal range. T-cell subsets among patients with ID revealed T-cell activation with a high percentage of HLA-DR antigen positivity, elevated CD4 ($2.4 \times 10^9/L$) and CD8 ($1.4 \times 10^9/L$) cell counts, with an increased CD4/CD8 ratio of 1:73.

Conclusion: Infective dermatitis is a distinct clinical entity associated with HTLV-I, which plays a role in the pathogenesis and immune perturbations observed.

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INFECTIONAL dermatitis (ID) in Jamaican children was first described by Sweet¹ in 1966, who noted a pattern of eczema in Jamaican children that was characterized by exudation and crusting around the nostrils, ears, and scalp with the eventual appearance of a generalized fine papular rash. The syndrome was quite different from any other infective eczemas he had seen in England and he was impressed by the speed with which cases responded to treatment with antibiotics and topical steroids. Additional cases were documented by Walshe² in 1967, when she established clinical criteria and described the bacteriological findings in 25 patients. Walshe postulated that these children might be immunosup-

pressed because of frequent relapses after definitive therapy, but the cause was not immediately apparent. In 1990, 14 cases of ID in Jamaican children

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were all reported to be positive for antibodies to human T-lymphotropic virus type I (HTLV-I).³ The current study was designed to compare patients with ID

*This article is also available on our
Web site: www.ama-assn.org/derm.*

PATIENTS AND METHODS

PATIENTS

Between December 1990 and August 1991, 50 patients with ID and 35 patients with AD older than 1½ years were selected consecutively from the dermatology and pediatric clinics of the University Hospital of the West Indies and the dermatology clinic of Bustamante Children's Hospital, Kingston, Jamaica. The criteria for diagnosis and enrollment of the 2 disorders in this study were based mainly on clinical findings.¹⁻⁴

Infective dermatitis was diagnosed based on the following criteria: (1) severe exudative dermatitis of the scalp, external ear and retroauricular areas, eyelid margins, paranasal skin, neck, axillae, and groin; (2) generalized fine papular rash; (3) chronic nasal discharge in the absence of other signs of rhinitis with crusting of the anterior nares; (4) cultures positive for *Staphylococcus aureus* or β -hemolytic streptococci from the anterior nares and/or skin lesions; and (5) prompt response to appropriate antibiotic therapy with subsequent relapse on withdrawal of therapy.

Diagnostic criteria for AD included the following: (1) chronic relapsing dermatitis with itching; (2) skin involvement at elbow and/or knee flexures and dry skin (xeroderma); and (3) personal or family history of atopy. Elevated IgE levels were considered suggestive of but not essential to the diagnosis of AD. Patients with the typical features of ID and AD are shown in **Figure 1** through **Figure 4**.

The cases of ID included children (aged 16 years and younger) as well as 7 adult patients aged 17 to 37 years who had been diagnosed in childhood and still attended the University Hospital of the West Indies dermatology clinic. These were compared with consecutive patients with AD evaluated in the clinic at the same time. With the consent of the patient, parent, or guardian, a blood sample, skin test, and skin and lymph node biopsy specimens (when clinically indicated) were obtained.

LABORATORY STUDIES

Peripheral blood mononuclear cells were separated by density gradient centrifugation, washed, and stored in 5×10^6 -cell aliquots using controlled rate freezing. Serum samples were obtained using appropriate blood collection tubes. Swabs for bacterial culture were used to collect exudate from anterior nares and skin lesions and 4-mm punch biopsy skin specimens were obtained for histological

examination. Lymph node aspirate or biopsy specimens were obtained from patients with palpable lymph nodes. Stool samples were collected for parasite evaluation. All serum samples, cells, swabs, biopsy specimens, and stool material were stored at -70°C until retrieved for testing.

Hematologic analysis included complete blood cell count with differential white blood cell count (WBC) and erythrocyte sedimentation rate. Erythrocyte sedimentation rate was adjusted for hemoglobin level. Serum protein electrophoresis was used to measure albumin levels and globulin fractions. Stool samples were examined for parasites, ova, and cysts. Serologic determination of antibodies for HTLV-I and human immunodeficiency virus 1 used whole-virus enzyme immunosorbent assays (DuPont, Wilmington, Del), and seropositive samples were confirmed using Western blot analysis (Cambridge-Biotech, Rockville, Md). Tissue specimens for histological examination were stained with routine hematoxylin-eosin. Enzyme immunoassay (Quantizyme, Kallestad Diagnostics, Austin, Tex) was used to determine serum IgE levels, and a radial diffusion method (Endoplate-m, Kallestad Diagnostics) was used to determine IgA, IgM, IgG, and IgD levels. Serum complement levels (Kallestad Diagnostics) were also measured. A multitest system (Institute Meriere, Lyon, France) was used to test for delayed hypersensitivity. Fluorescent antibody testing was used to measure lymphocyte populations and subsets (fluorescent activated cell sorter, FACSCAN, Becton Dickinson, Mountainview, Calif). Absolute lymphocyte subset counts were calculated based on total lymphocyte count.

STATISTICAL METHODS

Demographic characteristics of the study groups were analyzed using a *t* test to compare mean ages and a χ^2 or Fisher exact test to compare categories of age (<6 or ≥ 6 years) and sex. Skin and lymph node variables were examined using a χ^2 or Fisher exact test. Because a significantly greater proportion of patients with ID were older than the median age (6 years) of patients with AD, analysis of hematologic and biochemical factors used the Mantel-Haenszel χ^2 test adjusting for age as a dichotomous variable. Analysis of continuous values for immunoglobulins and T-cell subset variables was performed using generalized linear models that adjusted for age. Log transformation of immunoglobulins and T-cell subsets was used to obtain approximately normally distributed variables. All mean values presented in the Tables represent geometric means. All analyses were performed using a statistical analysis software system (SAS Institute, Cary, NC).

with patients with atopic dermatitis (AD), confirm the association of ID with HTLV-I, further define the clinical and laboratory features of the syndrome, and search for pathogenic clues.

RESULTS

The mean ages for the patients with ID and those with AD were similar: 6.9 years (range, 1-32 years) and 7.8 years (range, 1-36 years), respectively ($P=.15$). However, a significantly greater proportion of patients with ID (38 [76.0%] of 50) were aged 6 years or older com-

pared with patients with AD (18 [51.4%] of 35) ($P=.02$). The distribution by sex was comparable for the 2 groups, with 20 males (40%) in the ID group and 17 males (49%) in the AD group ($P=.43$).

In both groups, microbiologic studies showed frequent colonization with *S aureus* or β -hemolytic streptococci. Of the 47 patients with ID who were evaluated, 23 (49%) had cultures positive for *S aureus* and/or β -hemolytic streptococci on culture of swabs from the anterior nares, while 9 (30%) of 30 evaluated patients with AD had cultures positive for *S aureus* and/or β -hemolytic streptococci ($P=.10$). Culture of swabs from skin



Figure 1. Patient with a severe case of infective dermatitis with nasal discharge and crusting of anterior nares.



Figure 3. Patient with generalized fine papular rash associated with infective dermatitis.

lesions were positive for 1 or both of these organisms in 27 (59%) of 46 patients with ID compared with 13 (45%) of 29 patients with AD ($P=.24$). The results of stool microscopy were positive for ova, cysts, or parasites in 15 (44%) of 34 patients with ID and 5 (26%) of 19 patients with AD ($P=.20$). The predominant patho-

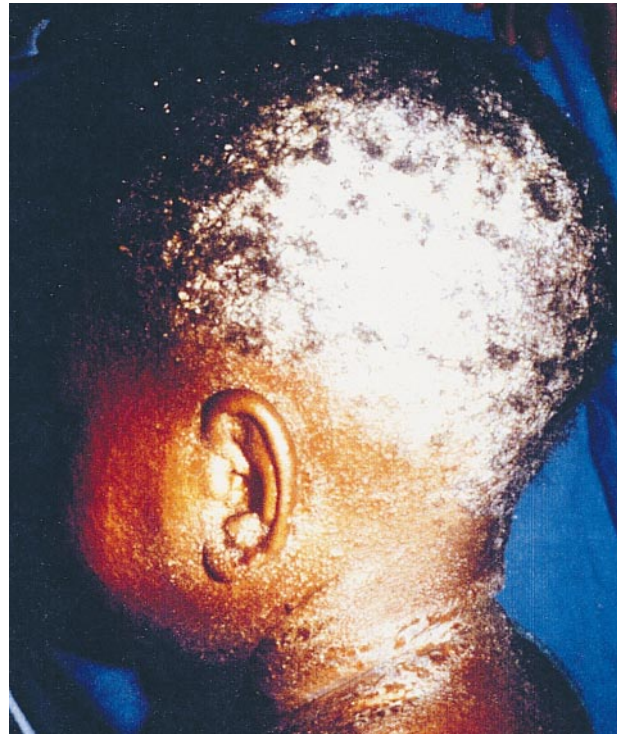


Figure 2. Patient with infective dermatitis with crusting of the scalp and exudative eczema of the neck, external ear, and retroauricular areas.



Figure 4. Patient with typical case of atopic eczema with flexural dermatitis.

genic organisms identified were Nematoda (*Ascaris*, *Ancylostoma*, and *Trichuris*) and Protozoa (*Giardia lamblia*).

The histological evaluation of skin biopsy samples showed similarly high prevalences of chronic dermatitis in both groups ($P=.74$). Palpable lymph nodes were present in a significantly greater proportion of patients with ID (24 [49%] of 49) than those with AD (6 [17%] of 35) ($P=.005$). Palpable lymph nodes were not determined for 1 patient with ID. Histological review determined these nodes to be dermatopathic lymphadenitis in 16 (67%) of 24 patients with ID compared with 1 (17%) of 6 patients with AD ($P=.04$).

The results of hematologic and biochemical parameters for the 2 patient groups are shown in **Table 1**. All 50 patients with ID had results seropositive for HTLV-I infection compared with 5 (14%) of the 35 patients with AD ($P<.001$), while the results were negative for hu-

Table 1. Hematologic and Biochemical Parameters Among Patients With Infective Dermatitis (ID) and Atopic Dermatitis (AD)*

Variable	No. (%) of Patients		P
	ID	AD	
HTLV-I status			
Positive	50 (100)	5 (14)	<.001
Negative	0 (0)	30 (100)	
Hemoglobin level, g/L			
120-150	9 (21)	13 (47)	.01
<120	35 (79)	15 (53)	
ESR, mm/h			
0-20	19 (43)	22 (73)	.03
20-50	13 (29)	8 (27)	
>50	12 (27)	0 (0)	
WBC count, $\times 10^9/L$			
<5	2 (5)	2 (7)	.08
5-10	26 (59)	20 (74)	
>10	16 (36)	5 (19)	
Total lymphocytes, $\times 10^9/L$			
≤ 4.0	14 (33)	15 (58)	.01
>4.0	28 (67)	11 (42)	
Total eosinophils, $\times 10^9/L$			
<0.40	24 (65)	8 (38)	.05
≥ 0.40	13 (35)	13 (62)	
Total protein level, g/L			
<68	5 (10)	6 (17)	.13
68-84	24 (49)	24 (69)	
>84	20 (41)	5 (14)	
Albumin level, g/L			
<38	10 (20)	1 (3)	.06
38-52	39 (80)	34 (97)	
Globulin level, g/L			
18-38	23 (47)	28 (80)	.02
>38	26 (53)	7 (20)	
Increased γ -globulin level			
Absent	28 (61)	31 (94)	.001
Present	18 (39)	2 (6)	

*HTLV-I indicates human T-lymphotrophic virus type I; ESR, erythrocyte sedimentation rate; and WBC, white blood cell. P values obtained from Mantel-Haenszel χ^2 adjusting for age (<6 years vs ≥ 6 years). Due to missing values, some columns do not equal total number of subjects. Erythrocyte sedimentation rate was adjusted for hemoglobin level. γ -Globulin level was a qualitative assessment.

man immunodeficiency virus 1 for all the patients in the study. The median HTLV-I antibody titer among the ID group (1:36 827) was significantly higher ($P<.001$) compared with the patients with AD who had results seropositive for HTLV-I (1:1580) after adjustment for age. Significantly more patients with ID than those with AD had anemia (hemoglobin level, <120 g/L; $P=.01$). White blood cell counts tended to be higher among patients with ID than those with AD ($P=.08$), and lymphocytosis was significantly more common among the patients with ID (67%) than those with AD (42%) ($P=.01$). Atypical lymphocytes were detected in 10 (22%) of the 45 patients with ID, but this was only slightly more frequent than in the patients with AD (5 [14.3%] of 35) ($P=.27$). Eosinophilia was more common among the patients with AD (62%) than those with ID (35%) ($P=.05$), with mean total eosinophil counts of $0.65 \times 10^9/L$ and $0.45 \times 10^9/L$, respectively.

Table 2. Immunologic Parameters Among Patients With Infective Dermatitis (ID) and Atopic Dermatitis (AD)*

Variable (Normal Range)	Mean Levels		P
	ID	AD	
Immunoglobulins			
IgA (52-235 U/mL)	205.75	85.87	<.001
IgD (0-14 mg/L)	58.19	25.15	.02
IgE (<163 U/mL)	229.11	268.17	.60
IgG (65-203 U/mL)	196.34	157.34	.01
IgM (50-280 U/mL)	165.21	141.05	.28
T-Cell Subsets			
HLA-DR, % (range)	30.93 (8-68)	9.56 (3-26)	<.001
CD4 (range)	2399.20 (800-7326)	1257.77 (225-3916)	<.001
CD8 (range)	1386.96 (242-5488)	969.28 (99-3424)	.04
CD4/CD8 (range)	1.73 (0.39-6.75)	1.29 (0.49-4.0)	.05

*P values were derived from linear regression models that included adjustment for age. Values for ID and AD are the geometric mean. Values for CD4 and CD8 are absolute numbers.

An elevated erythrocyte sedimentation rate was observed in more patients with ID than in those with AD even after adjustment for hemoglobin levels ($P=.03$). Elevated serum globulin and γ -globulin levels were more prevalent in patients with ID compared with those with AD ($P=.02$ and $P=.001$, respectively). Elevated serum protein levels also were detected in a greater proportion of patients with ID than in those with AD, although this association was not significant after adjustment for age ($P=.13$). A slightly higher proportion of patients with ID had low albumin levels ($P=.06$).

Numerous indicators of B- and T-cell activation were evident among patients with ID (**Table 2**). Levels of several immunoglobulin classes (IgD and IgE) were elevated among patients with ID and those with AD above the upper limit of the normal range. There were significant increases among patients with ID compared with those with AD for IgA, IgD, and IgG levels ($P<.001$, $P=.02$, and $P=.01$, respectively). Both groups had similarly elevated IgE levels, while patients with AD had mean levels of IgA, IgG, and IgM within normal limits. There was no deficiency of complement detected in either group (data not shown).

Patients with ID had a significantly higher level of activated HLA-DR⁺ lymphocytes compared with patients with AD (Table 2) ($P<.001$). A significantly higher mean CD4 cell count among patients with ID resulted in an elevated CD4/CD8 ratio of 1.73 compared with 1.29 among patients with AD ($P<.001$ and $P=.05$, respectively). Circulating absolute mean CD8 cell counts were significantly higher ($P=.04$) in patients with ID as well. Skin tests for delayed hypersensitivity were reactive for at least 1 antigen in all patients tested in both groups, indicating that no patient was anergic (data not shown).

We looked more closely at the 5 patients (14%) with AD seropositive for HTLV-I to see if they resembled the patients with ID or those with AD seronegative for HTLV-I. With respect to clinical and laboratory parameters, they resembled the patients with AD seronegative for HTLV-I except for slightly lower mean hemoglobin levels.

Human T-lymphotrophic virus type I is the causal agent for adult T-cell leukemia or lymphoma (ATL), an aggressive T-cell lymphoma, and HTLV-I-associated myelopathy, also known as tropical spastic paraparesis (HAM/TSP), a chronic neurodegenerative disease.⁵ Human T-lymphotrophic virus type I and its related diseases cluster in virus-endemic areas of southern Japan, the Caribbean, parts of Africa and South America, and the Melanesian Islands. The virus has also been identified in the United States and other locales, primarily among migrants from endemic areas. Human T-lymphotrophic virus type I is transmitted horizontally by parenteral (contaminated needles or transfusion) or sexual contact and from mother to infant by breast-feeding. Among HTLV-I carriers, less than 5% of individuals develop ATL or HAM/TSP and there is usually a long latency of decades between infection and subsequent development of disease, with the exception of transfusion-associated HAM/TSP, which can develop several weeks to months following infection from contaminated blood components. However, there have been only rare reports of ATL and HAM/TSP among children.^{6,7} The seroprevalence of HTLV-I among children aged 1 to 9 years and 10 to 19 years is about 1% and 1.44% for each age group, respectively, in endemic areas.^{8,9}

In our pilot study reported in 1990,³ we suggested a link between HTLV-I and the childhood disorder ID. We have now confirmed this relationship in a much larger number of patients with ID, all of whom are positive for HTLV-I and negative for human immunodeficiency virus 1 antibodies. This suggests an etiologic role for HTLV-I in ID. Interestingly, 5 (14%) of the 35 patients with AD had results seropositive for HTLV-I antibodies. This is higher than the HTLV-I seroprevalence rate (1%) for Jamaican children.⁸ However, the viral antibody titers of the patients with AD who were positive for HTLV-I were significantly lower than the titers in the patients with ID. It may be that HTLV-I plays a role in the development of dermatitides other than ID including AD or, conversely, that there are milder cases of ID with clinical features that resemble AD. Our findings support the first hypothesis, since the clinical and laboratory results of the 5 patients with AD who were seropositive for HTLV-I were generally similar to the results of patients with AD rather than ID. Patients with AD are known to have alterations in host defense mechanisms making them susceptible to infections, partly because of the presence of mild immune dysfunction.⁴ However, if there are milder cases of ID misdiagnosed as another type of dermatitis, HTLV-I seropositive status can be used to increase the sensitivity of detecting such cases.

We were not surprised that the histological characteristics of the skin in the results of routine histological examination with hematoxylin-eosin staining did not differ significantly between ID and AD. They are both clinical types of dermatitis, and the histological characteristics of dermatitis are essentially the same, regardless of the cause. Bacteriological results presented herein underestimate the true picture of bacterial colonization of skin and anterior nares infection in these patients, since

many patients had already started antibiotic treatment at the time of evaluation, which would certainly affect the results. However, our results do indicate that both patients with AD and those with ID are prone to infections with *S aureus* and β -hemolytic streptococci.

We have now clearly documented that when compared with children with AD, children with ID are anemic and have higher WBC counts, lymphocytosis with circulating atypical lymphocytes, and higher erythrocyte sedimentation rates. This is in keeping with the inflammation attributable to the relapsing, chronic bacterial infection that is the basis of ID and the increased morbidity associated with this disorder. However, it could also be argued that anemia may be associated with the HTLV-I seropositive status of the patients with ID rather than the disease because this association has been previously reported in adult HTLV-I carriers.¹⁰ We were unable to characterize the type of anemia, thus limiting our ability to determine whether it was a result of chronic inflammation or nutritional deficiency. Previously, anemia in patients with ID had been characterized as an iron deficiency.²

The role of poor nutritional status in the pathogenesis of ID was previously suggested because patients often presented with a constantly dripping nose without other signs of rhinitis. In many respects, this resembled a sign of edema due to hunger that is seen in patients with protein energy malnutrition.² It is our distinct impression that patients with ID are of lower socioeconomic status. Therefore, the low serum albumin levels seen among patients with ID in our study may reflect either a nutritional deficiency or a reduced absorption in the presence of chronic infection and parasitic infestation. Low serum albumin levels have also been reported among adult HTLV-I carriers.¹¹ We did not detect abnormal albumin levels among the patients with AD with seropositive HTLV-I status.

The elevated serum globulin levels among patients with ID reflect the increased immunoglobulin levels that we have demonstrated. This is not believed to be an effect of HTLV-I infection because adult HTLV-I carriers are reported to have impaired immunoglobulin production.¹² It is well known that elevated serum IgE levels are seen in as many as 80% of patients with AD.⁴ In fact, it is regarded as a major diagnostic criterion, and defective IgE regulation is important in the pathogenesis of AD.⁴ Yet serum IgE levels were similarly elevated in both groups. Decreased IgE levels have been reported among adult HTLV-I carriers.¹³ Thus, the IgE overproduction we observed and other hyperimmunoglobulinemia in patients with ID may reflect chronic antigenic stimulation or a generally hyperactive immune system that may be important in disease pathogenesis.

Cell-mediated immunity was intact among our patients with no evidence of anergy in the results of skin testing. Previous reports⁴ have suggested that anergy and low levels of circulating CD8 cells are a feature of AD. In our examination of T-cell subsets, the CD4/CD8 (helper-suppressor) T-cell ratio was increased in patients with ID compared with those with AD. This reflects primarily an increase in the CD4⁺ (helper) T cells. An increased CD4/CD8 ratio has also been reported in

Table 3. Characteristics for Diagnosis of Infective Dermatitis**Major***

1. Eczema of scalp, axillae and groin, external ear and retroauricular areas, eyelid margins, paranasal skin, and/or neck
2. Chronic watery nasal discharge without other signs of rhinitis and/or crusting of the anterior nares
3. Chronic relapsing dermatitis with prompt response to appropriate therapy but prompt recurrence on withdrawal of use of antibiotics
4. Usual onset in early childhood
5. Human T-lymphotrophic virus type I antibody seropositivity

Minor or less specific

- Positive cultures for *Staphylococcus aureus* and/or β -hemolytic streptococci from the skin or anterior nares
- Generalized fine papular rash (in most severe cases)
- Generalized lymphadenopathy with dermatopathic lymphadenitis
- Anemia
- Elevated erythrocyte sedimentation rate
- Hyperimmunoglobulinemia (IgD and IgE)
- Elevated CD4 count, CD8 count, and CD4/CD8 ratio

*Of the 5 major criteria, 4 are required for diagnosis with mandatory inclusion of 1, 2, and 5; to fulfill criteria 1, involvement of at least 2 of the sites is required.

otherwise asymptomatic adults with seropositive HTLV-I status,¹⁴ so this finding could relate solely to HTLV-I infection rather than ID per se. Similar to children who are asymptomatic with seropositive HTLV-I status,¹⁵ several patients with ID had an increased proportion of activated (HLA-DR⁺) T cells. The similarity of these findings to children and adults who are asymptomatic and carriers of HTLV-I suggests that the T-cell subset changes we observed are primarily due to HTLV-I infection.

It is well known that the response to many infections is genetically determined and familial ID has been reported.^{2,16} Studies of HLA in HTLV-I endemic populations seem to suggest that there are genetic differences between people who develop ATL and those who develop HAM/TSP.¹⁷ So the type of HTLV-I-related disorder that develops among HTLV-I carriers may at least in part be genetically determined. We have already reported the first documented case of ATL developing in a patient with ID after 17 years,¹⁸ and we have also reported the occurrence of 2 cases of HAM/TSP developing in patients with ID after 12 and 25 years.⁷

This study confirms the association between HTLV-I infection and ID in Jamaican children. Additionally, it demonstrates that ID is not only a marker for childhood HTLV-I infection, but also a disease entity in its own right and a possible harbinger of more serious HTLV-I-associated disorders in later life. We have refined the diagnostic criteria for ID (**Table 3**). Of the 5 major criteria, 4 are required for diagnosis and must include criteria numbers 1, 2, and 5. The areas of skin involvement include eczema of the scalp, axillae and groins, external ear and retroauricular areas, eyelid margins, and paranasal skin and/or neck. Involvement of at least 2 of these sites is required. We believe that HTLV-I-associated ID represents a more severe type of ID because dermatologists regularly diagnose other, less severe, nonrelapsing types of ID. Since our initial report, similar cases of ID

in HTLV-I-infected children have been reported from Trinidad, Colombia, Japan, and Brazil, which are known HTLV-I endemic areas.¹⁹⁻²² We propose the new designation, HTLV-I-associated ID, to identify such cases and differentiate this type from other types of ID.

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